Anatomy of handedness and the laterality of seizure onset: surgical implications of new understandings in motor control

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Objectives: This article pursues another corollary of the anatomy of handedness, a code for the laterality of motor control. The latter indicates the absence of any motor communication from the minor (right, in the vast majority of population) to the major hemisphere (left, in the vast majority of right handers). It also indicates that all communications between the two hemispheres are excitatory in nature. This arrangement prohibits initiation of seizure within the minor and its propagation to the major hemisphere, via the callosum.

Methods: A comprehensive review of the literature is undertaken regarding theoretical and technical reasons for the failure of seizure surgery in subjects undergoing the same for intractable epilepsy.

Results: Whereas the laterality of motor control is heavily biased towards the left hemisphere (~80%), the operation is performed equally on both hemispheres. Failures of surgery in some series were substantially higher among those who had undergone operations on the right hemisphere. Technical reasons for this are traced to the unreliability of tests commonly employed in securing laterality of seizure onset, which is the same as that of motor control. Accordingly, the failure rate of seizure surgery may equal the rate of false lateralization of the major hemisphere in these circumstances.

Conclusion: Given the dichotomous anatomy of handedness, the most robust test for lateralizing the hemisphere of onset of seizure is that of determining the reaction times of two symmetrically located effectors, one on each side of the body. The side with the shorter reaction time will always be opposite to the major hemisphere. The difference between the two values is commensurate to the inter-hemispheric transfer time. [Neurol Res 2005; 27: 773–779]

Keywords: Epilepsy surgery; motor control; false lateralization; neural handedness

INTRODUCTION

One-way callosal traffic pathway, which underpins the laterality of motor control, negates the possibility of initiation and generalization of seizures from the minor hemisphere (except in circumstances like increased intracranial pressure). This is because motor traffic between the two hemispheres is one-directional, from the major to the minor hemisphere: a directionality that is coded as (neural) handedness (see below). Thus, as all commands are initiated in the major/executive hemisphere (left, in right handers), and those taking place on the non-dominant side are implemented by the minor, moving the non-dominant side is a bi-hemispheric event requiring callosal participation1–7. The reverse occurs in (neural) left handers. There is 80–85% congruence between neural and behavioral handedness in the general public, the remainder enjoying an ostensible handedness, which may go unrecognized throughout their lives or become manifest as one of several crossed syndromes known to neurologists and neurosurgeons for more than a century (see below for further explanation)1–7.

The facts denoting bi-hemispheric activation of the brain on moving the (neurally) non-dominant hand have been independently confirmed numerous times, in both motor and sensory realms3,5,6. These were most recently reviewed by Haaland et al., who concluded that ‘consistent with data in brain damaged patients, the left dorsal and parietal areas are engaged when advance planning is required to perform complex motor sequences that require selection of different effectors and abstract organization of the sequence, regardless of the performing hand’10. According to the new scheme under review, the directionality of callosal traffic in the sensory domain is the opposite of that in the motor (from the right to the left hemisphere, in right handers), with fibers carrying sensory signals from the non-dominant side of the body occupying the posterior aspect of the callosum1,9–13. It should be emphasized that the executive hemisphere manages speech and other movements14–17. The fact that verbally and manually expressed languages (as in sign language) are similarly affected in disease states testify to the closeness of the anatomical relationship between speech and hand movements (see below for further explanation)14–17.
The present article pursues an important corollary of directionality in callosal traffic sketched above, i.e. the distribution of onset (lead) hemisphere initiating seizures with secondary generalization; resulting in grand mal and impaired consciousness.

METHODS
A comprehensive search of the literature points to the following syndromes as evidence for directionality in inter-hemispheric transfer in humans. Some of these syndromes are well known in clinical neurology (a–c), while others have come to light as a result of the insight gained from the new scheme delineated above (d–f).

(a) 'Apraxia' on the non-dominant side, documented in callosal transections (natural or iatrogenic), resulting in a separation shock (diaschisis, motor deafferentation) in the minor hemisphere, which in turn is manifested as the inability to move the hand ipsilateral to the major hemisphere upon command (the left in right handers)\(^1\)–\(^3\).

(b) Ipsilateral weakness/apraxia occasionally seen in lesions affecting the major hemisphere, often misinterpreted as the effect of Kernohan notch\(^1\)–\(^2\).

(c) Immediate but temporary improvements of neglect upon using the non-dominant hand in lesions affecting temporoparietal lobes of the minor hemisphere, brought about by the excitatory influences of the command signals originating in the major hemisphere to move the left hand (signals transmitted to the minor hemisphere via the callosum)\(^1\)–\(^2\),\(^18\).

(d) Delayed (time consuming) improvement of the activity of the non-dominant hand in lesions affecting the major hemisphere, reflecting the time required for re-establishment of the severed callosal connections between the major and the minor hemisphere\(^7\).

(e) Worsening of the weakness of the non-dominant side of the body due to an earlier lesion in the minor hemisphere when a new lesion occurs in the contralateral (major) hemisphere, deafferenting the minor hemisphere and thus increasing the weakness\(^5\)–\(^7\),\(^9\)–\(^11\).

(f) Switching of the hitherto favorite hand in those with ostensible/behavioral handedness (versus neural), following transection of the callosum. This results from the separation of the favorite (but neurally non-dominant) hand from the major hemisphere, rendering it out of volitional control, hence the switch to the previously non-dominant hand that had retained its connection to the major hemisphere and was thus available to the subject after callosotomy\(^22\)–\(^26\).

Experimentally, evidence for callosal participation in the above syndromes may be summarized, as follows.

(a) The extra time needed to move effectors on the non-dominant side of the body, commensurate to the interhemispheric transfer time (IHTT)\(^1\)–\(^3\),\(^8\).

(b) That moving the non-dominant side of the body is a bi-hemispheric event requiring callosal participation, documented in EEG, magnetic encephalography (MEG) and other emission studies\(^8\),\(^27\)–\(^30\).

(c) Unalterability of the ipsilateral silent period (ISP) and reaction time of the ‘mirroring’ right hand on transcranial magnetic stimulation (TMS) of the minor (right) hemisphere\(^31\), indicating the impermeability of the major hemisphere to the events occurring in the minor; and the larger SP in the muscles of the non-dominant hand when the command initiated in the major hemisphere (for both sides, as mentioned above) is interrupted by TMS; the latter reflecting the IHTT related to the callosally mediated delay in resuming previous activity\(^32\)–\(^35\). (d) Speech is only one among other motor activities controlled by the major hemisphere, albeit one that readily marks the hemisphere in which it resides as the executive/major hemisphere (hemisphere of action)\(^8\),\(^14\).

(e) Tactual threshold of simultaneity is longer on the non-dominant side by an amount commensurate with IHTT\(^36\).

RESULTS
The above indicates that moving the non-dominant side requires participation of both hemispheres. Expressed differently, there is a sharing of resources within the left (major) hemisphere when moving the left side of the body. This was documented recently in a timed video-recording of a right hander with watershed ischemic lesions affecting callosal fibers after they had crossed into the minor hemisphere; showing downward drifting of the outstretched left arm as the patient moved the right, whereas the right arm was stable when the patient moved the left in the same manner, demonstrating the asymmetrical traffic mentioned above\(^7\).

DISCUSSION
Handedness, behavioral versus neural
Taking account of the fact that there has never been a verifiable explanation for crossed non-aphasia and crossed aphasia (respectively, syndromes in which aphasia did not occur when expected or that it did unexpectedly occur—given the behavioral handedness of the subject on both occasions), it is evident that a distinction must be made between behavioral and neural handedness in order to explain such syndromes. According to the new scheme\(^1\)–\(^2\), such a distinction lies behind these occurrences, belying biological relevance of behavioral handedness. Neural handedness, on the other hand, has biological/anatomical relevance as it represents the unchangeable (hard-wired) proximity of the dominant side of the body to the command center in the major hemisphere—by a callosum width/length (compared with the non-dominant side). Accordingly, the avowed handedness reflects habitual use of one hand for doing things in daily life; it is a phenomenon reflecting the combined effects of neural wiring and the availability of choice to all of us to employ either hand for getting things done\(^3\) regardless of the acceptability of the performance, and the social norms of the society.

The following observations further underscore the need to revise our view of the behavioral handedness in favor of the neural when considering generalization of seizures.
(a) There are scores of inventories for classifying humans as to their behavioral handedness, a *prima facie* evidence of the arbitrariness of all such inventories.

(b) The freedom we have to use either hand in performing a task as mentioned earlier.

(c) The occurrence of crossed syndromes, indicating inseparability of the ability to talk and the machinery of executive functions, regardless of the behavioral handedness of the subject.

Clinically, this is manifested by the fact that, given a large enough lesion in the major hemisphere, whenever the speech goes so does the ability to control the neurally dominant side of the body (demystifying the crossed syndromes mentioned earlier).

There is strong evidence indicating that onset and generalization of epilepsy has the same distribution among epileptics as that of (neural) handedness in the public (i.e. it is heavily skewed to the left by ~80/20)37–40. Experimentally, this is corroborated by studies employing coherence phase analysis (cross-correlation function) of spike–dome discharges arising from homologous derivation of the scalp, showing the lead of one hemisphere in generating ictal and interictal spikes prior to the involvement of the homotopic region in the other hemisphere after an interval commensurate with IHTT, producing bursts of bilateral ‘synchronous’ spike–wave activity (BSSW)41–44. Depending on the neural handedness of the subject, either the left or the right hemisphere initiates the seizures, but never both44.

Given the above considerations, similarity of binomial distribution of (neural) handedness and laterality of the lead hemisphere in epilepsy is a significant finding, bolstering the veracity of the newly described anatomy as well as pointing out a possible reason for the reported failures of surgery in a substantial minority of those who undergo operations for removing the offending focus (failures related to false lateralization of the major hemisphere).

Binominal distribution of neural handedness is discernable in many ways. Accordingly, the easiest is to determine the reaction time of each hand using any of the variations of Poffenberger’s paradigm. The simplest demonstration of this is simultaneous snapping of the fingers of both hands, which produces two clicks, the first one from the neurally dominant hand, because of its direct connection to the major hemisphere (see above). This experiment demonstrates the inability of humans to aim at two targets with both hands at the same time and has been known to musicologists for more than a century. The latter refer to it as ‘the melody-lead of the right hand’, and ascribe it to ‘artistic expression’. Such experiments, however, corroborate Liepmann’s view as to directionality in callosal traffic shown in his drawings (Figure 1).

The newly described pathway provides a different interpretation for the results of earlier lateralized reaction time studies45–48, by recognizing the role of laterality in motor control as it relates to macular vision: as the latter is the province of the major hemisphere2. It attributes the longer reaction time of the non-dominant hand solely to the directionality in callosal traffic1–2. At the same time, the larger tactual than visual ‘crossed uncrossed difference’ (i.e. the difference between right and left hand reaction times to foveal stimuli) confirms the existence of directionality in callosal traffic in the sensory realm48.

Furthermore, evidence from the time-resolved experiments mentioned above2, and from functional equivalents in emission and Doppler imaging techniques49,50 has shown that binomial distribution of neural handedness in general population is ~75–80% in favor of the left hemisphere/right hand (i.e. the incidence of neural
left handedness in general population is ~20–25%). How this compares with the data available for epilepsy? Before entering the latter consideration one must be mindful of several caveats. First, is the definition of seizure for the purpose at hand. As the aim is to identify (lateralize) the major hemisphere as the source of seizures (interfering with speech or awareness), symptoms like grand mal or complex partial seizures will be of interest. Secondly, as the interest is in lateralizing the source of seizures, lateralization takes precedence over the exact localization of the source in the major hemisphere.

A review of the subject suggests that, like the reaction time, the crossed uncrossed differential and the SP’s duration, the distribution of interictal epileptiform discharges (IEDs) may also be used as the surrogate for the laterality of the hemisphere in which seizures are inaugurated (see below). Thus, given the insight from the one-way callosal traffic scheme (i.e. the absence of motor communication from the minor to the major hemisphere), it appears that determination of neural handedness of a patient has the same import as lateralization of initiating (lead, major) hemisphere in seizures affecting the speech or awareness.

Three large-scale studies may be cited in support of the above statement

Among 671 EEGs of right-handed epileptics (from a pool of 8500 epileptic subjects) with epileptic discharge restricted to the right \( (n=276) \) or left hemisphere \( (n=395) \), Manaut et al. encountered ictal linguistic disturbances in 35% of subjects with right hemispheric discharge compared with 65% in those with discharge restricted to the left hemisphere. In another study involving 184 consecutive patients with temporal lobe epilepsy (TLE), left/right (or left>right) lateralization of seizures occurred in 63/37 and 76/24% of patients, as reported by Cendes and colleagues. Lastly, in a study of 152 children with intractable epilepsy, employing Wada memory asymmetry for lateralizing seizure onset, Lee and colleagues found a left/right hemisphere ratio of 94/58 (62 versus 38%). Notwithstanding the known vagaries of EEG and Wada test in lateralizing motor control/seizure onset, the above data is in line with the statistics given earlier; confirming that it is the major hemisphere that initiates seizures, with a distribution similar to that of neural handedness. Given the above, the extent of failure to lateralize the lead hemisphere in patients undergoing epilepsy surgery is reflected in the large minority who continue to experience auras (which by some accounts is the same as having seizures for the cessation of which the patients underwent surgery) or actual seizures after one or more attempts to remove the offending site(s). The fact that all such series have consistently shown roughly similar numbers of operations on the left and right hemisphere strengthens the above suspicion, pointing to the use of techniques of doubtful reliability for determining the ‘lead’ of the hemisphere hosting the focus.

In the same vein, the controversial issues of ‘independent epileptiform activity’, ‘mirror focus’, ‘bilateral temporal lobe epilepsy’, all find a verifiable resolution in the one-way callosal traffic scheme, all pointing to the theoretical and methodological weaknesses involved in such determinations; i.e., they are relics of lack of familiarity with the anatomy underpinning motor control and generating seizures.

Summing up, the theoretical reason for failures of surgery and re-operations in seizure surgery lies in the unbounded assumption of existence of reciprocity between homotopic regions of the two hemispheres, as conceptualized by von Monakow (Figure 2, A1), permitting belief in contralaterality of motor control in humans and in equal likelihood of initiation of seizures from both hemispheres and its generalization to the other. Modification of classical callosal traffic to account for neural handedness and laterality of hemispheric onset of epilepsy are depicted in Figure 2 (A2–3).

With regard to methodology, one can document (almost) universal employment of amplitude predominance in favor of temporal precedence in attempts to identify the hemisphere in which seizures start. Other reasons for failure may be enumerated as: variation of the sample size (duration of EEG recordings); rapid changes of amplitude asymmetry from one side to the other.
other while recording EEG (at times occurring within 1 minute)\textsuperscript{57}, lack of correlation between the number of IEDs originating from one side and the probability of detecting ‘independent’ IEDs on the other\textsuperscript{58}, variability of likelihood of propagation of seizure activity from the lead to the neighboring hemisphere versus the spread of seizure within the lead hemisphere\textsuperscript{59}, ‘statistical fluctuations’ in telemetric recordings and the obscuration of the onset by movement artifacts\textsuperscript{60}, the lack of resolution of the routine EEG in determining the time difference between two hemispheres\textsuperscript{61}, variation of conductivity of the skull due to natural or pathological causes\textsuperscript{62,64}, diversity of indices representing seizure activity (e.g., delta slowing versus spikes) as well as use of extra-electrodes\textsuperscript{65}, and inter-rater variance on the morphology of potentials and their lateralization\textsuperscript{66}.

The failure of surgery has been documented in 25\% of temporal lobe epilepsies even after entirely ‘successful lateralization’ of interictal spikes and sharp waves, using the amplitude criteria\textsuperscript{67}. The same failure rate was seen in patients with refractory extratemporal epilepsy that had shown ‘strictly unilateral unifocal discharges’ in repeated EEG recordings\textsuperscript{58}, both of these situations emphasizing the likelihood of false lateralization when using amplitude or mere presence of IEDs as markers for the laterality of seizure onset\textsuperscript{66,69,70}. The latter observation jibes well with the fact that in some series of re-operation for failed surgery the right hemisphere operations outnumbered the left by as much as two to one\textsuperscript{21} (24 versus 16, n=40) or three to one\textsuperscript{22} (14 versus 6, n=20). Similarly, 30\% of patients who underwent pre-surgical evaluations for resective surgery were ultimately disqualified for lack of clear localizing evidence\textsuperscript{73}. Relapses occurred at the rate of 22\% (exclusive of auras) in one prospective study and 27\% in a retrospective study, despite continued use of anti-convulsants after the surgery in both situations\textsuperscript{4,7}. In a span of five decades, Rasmussen reported ‘seizure free’ status only in a third of patients in a series numbering 1267 cases\textsuperscript{7}. Not surprisingly, the re-operations were usually performed on the same side as the first operation, majority of which having had depth electrode recordings.

Finally, instances of hemispherectomy at the second or third operation on the same side are on record without resulting in the cessation of seizures or the need to continue medication, signifying false lateralization of epilepsy at an extremely high cost\textsuperscript{22,76,77}.

CONCLUSION
With an estimated ‘seizure free’ rate of 60–65\% by ablative surgery\textsuperscript{55}, and an automatic chance of operating on the correct hemisphere at 50\% (according to the new scheme), the above analysis implies significant room for improvement in the results of such operations, if the correct hemisphere were chosen for the intended purpose. The facts presented above and the knowledge that resorting to invasive investigational techniques by itself predicts a poor outcome\textsuperscript{55} enhances the attractiveness of the above described simple but robust method to further improve the results of surgery for non-tumoral seizures that have proved resistant to medical treatment.

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